REMARKS

Claim 42 has been amended as suggested to meet the objection raised.

In response to the first issue raised under 35 USC 112 second paragraph, the order of the compounds listed has been amended to make clear that the only analogs contemplated are those of galanthamine and lycoramine and not those of rivastigmine.

In response to the second issue raised under 35 USC 112 paragraph 2, it has been made clear that the half life requirements set out in the claim apply to any centrally-acting acetylcholinesterase inhibitor that may be used in the composition.

All of the currently pending claims except for claims 20, 38 and 40 are rejected under 35 USC 103(a) over the combination of WO 88/08708, Reimann, Conte, Cummings and Ross. Claims 20 and 38 are rejected under 35 USC 103(a) over this combination further in view of Nordberg. Claim 40 is rejected over the same combination as claim 1 et al further in view of Kennedy.

The key issue therefore in all of the rejections is what can be derived from a proper understanding of the combined teachings of WO 88/08708, Reimann, Conte, Cummings and Ross.

As discussed previously, WO 88/08708 teaches away from it in placing emphasis on constant levels of active compound in the blood stream, which is precisely what the present invention aims to avoid. Riemann reports on the influence of galanthamine hydrobromide on REM sleep regulation in healthy volunteers. Conte describes press-coated tablets for time-programmed release of drugs with emphasis on release of drugs at

the proper rate and includes "psychotropic" drugs in a list of drugs that may be formuated in this way. Cummings is used by the examiner to interpret Conte in a way which is disputed by the applicant. Ross reports on the effects of night time administration of doepezil an Alzheimer's drug falling outside the definitions of the present claims because of its long half life.

The essential difference between the applicant and the examiner seems to be the examiner's view that the combined teachings of Ross, Riemann and Conte would lead one skilled in the art to go against the teachings of WO 88/08708 to keep the blood levels of acetylcholinesterase inhibitors constant, notwithstanding the fact that the half life of the most commonly used Alzheimer's drug, donepezil, is such that blood levels will nromally be quite constant if there is daily administration of the drug as is the norm.

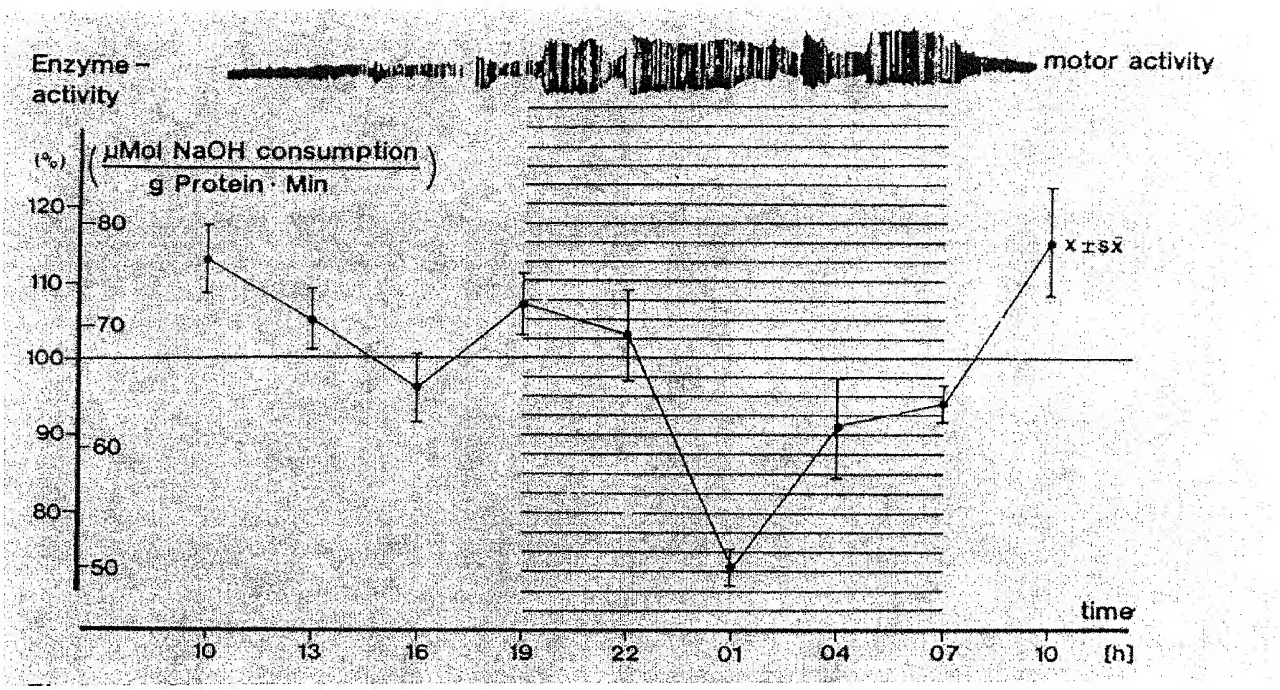
The key passage in the examiner's argument in support of this position seems to be at the bottom of page 10 of the present action:

> Ross *et al.* teach that administration of the acetylcholinesterase inhibitor donepezil at night produces results in insomnia and nightmares. The authors therefore suggest administration in the morning rather than at night. Reimann *et al.* teach that the cholinesterase inhibitor galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine. The skilled artisan would thus have found it obvious that morning administration of an acetylcholinesterase inhibitor could be readily obtained by providing a dosage form that could be administered at night *(e.g.,* before bedtime), but wherein the release of active agent is delayed until morning. Such delayed-release dosage forms are disclosed in Conte *et al.* Conte *et al.* provides methods of formulating compositions that will aid in patient compliance, *i.e.,* a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

The applicant comments on each of the references cited in this passage as follows:

Ross

As we disclosed in this patent application, acetylcholinesterase activity in mammalian brain as known to have a diurnal variation. Enzyme activity was low during the activity period, and high during the rest period, keeping synaptic acetylcholine low so that normal rest-period functions could occur.



The work of Scheibeler shown in the figure above, depicts the variation in acetylcholinesterase activity over the course of a day, relative to the 24 hour mean activity, which is the level of enzyme activity at the transitions between rest and activity periods.[1] During the rest period, which is the light phase in these rats, and corresponds to the minimal motor activity in the tracing at the top of figure, acetylcholinesterase activity is approximately 96% to 115% of the 24 hour mean.

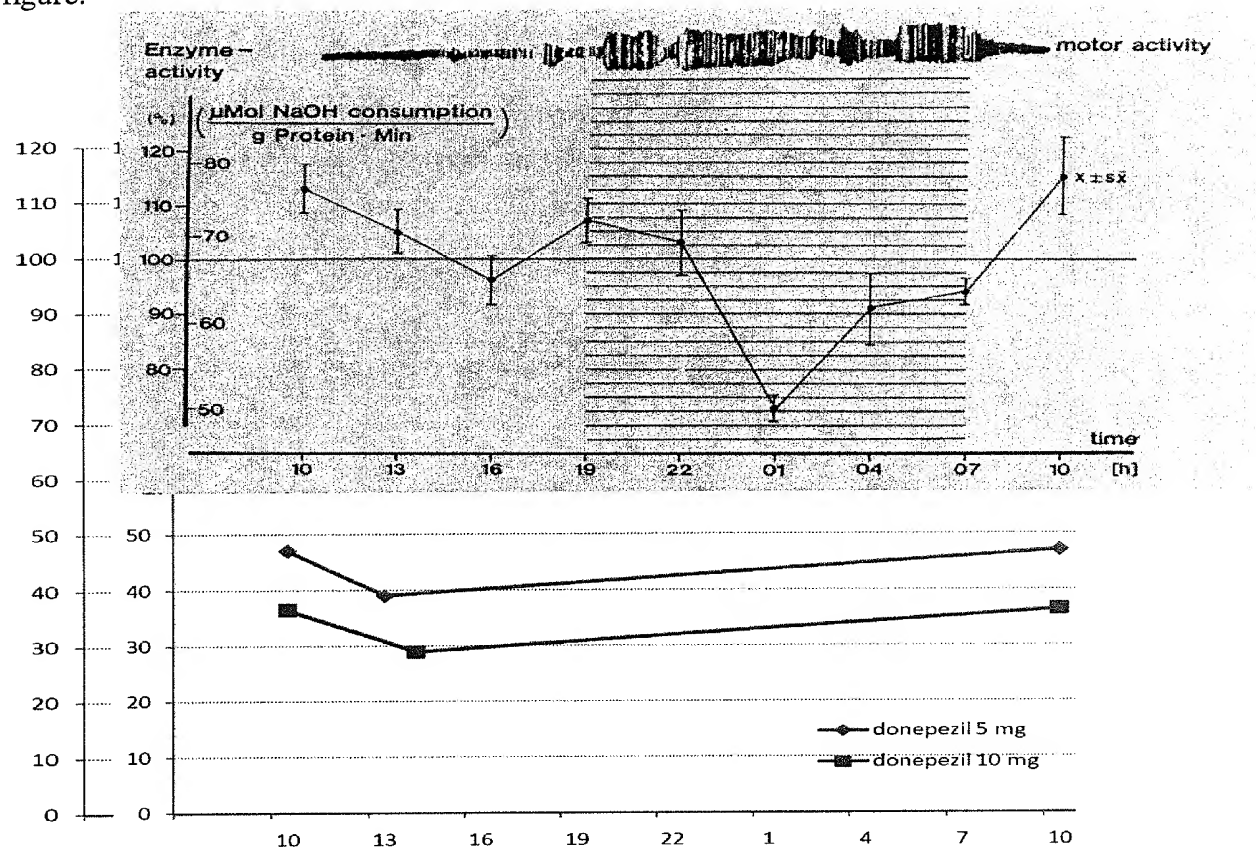
The acetylcholinesterase inhibition in red blood cells in humans taking 10 mg of donepezil daily varies from a daily low of 74.7 ± 4.4 to a high of 83.6 ± 1.9%.[2] In humans on 5 mg, the low is 62.2% and the high is 71.8%. The relationship between RBC and brain acetylcholinesterase inhibition following donepezil administration has been demonstrated

[1] Scheibeler, 1974, previously provided.

[2] Tiseo PJ, Rogers SL, Friedhoff LT, Pharmacokinetic and pharmacodynamic profile of donepezil HCl following evening administration. Br j Clin Pharmacol 1998; 46(Suppl. 1):13-18 (copy enclosed)

in rats. It is very strong (r= .94, n = 27).[3] The maximum inhibition in cortex is 15.2% less than the maximum inhibition in brain (69.2% vs 81.6%) Thus the enzyme inhibitions in brain in patients on 10 mg donepezil would be predicted to be 63.3 to 70.9%, and for 5 mg, 52.7 to 60.9%. Thus, the remaining acetylcholinesterase activity was 36.7 to 29.1% for 10 mg, and 47.3 to 39.1% for 5 mg, of the baseline, a 9 pm blood taken at the activity-rest transition in humans. That is more inhibition, at a minimum, than is normal for the *activity* period, when peak inhibition was about 30% at 01 h, and rats were quite active, as shown by the activity tracing. The enzyme is extraordinarily more active than during the normal rest period.

Thus, the acetylcholinesterase inhibition produced by donepezil, during the entire 24 hours after it is taken, is, literally, off the chart of a physiological diurnal variation in enzyme activity. Moreover, it is in the wrong direction. It exceeds the low activity needed for alertness on a continuous basis, in no way permitting the *increase* in enzyme activity to decrease acetylcholine as is needed for the rest period. This is illustrated below in the figure:



[3] Sherman KA, Pharmacodynamics of oral E2020 and tacrine in humans: novel approaches. In Cholinergic Basis for Alzheimer Therapy, R Becker and E Giacobini, Eds,, Birkhauser Boston, 1991, pp 321-328.

Comparison of circadian physiological changes in acetylcholinesterase activity in mammalian brain with acetylcholinesterase activity following donepezil administration at 10 pm. Percentage changes in enzyme activity from the rest-activity phase transition periods are shown on the y axis. 24 hour clock time is shown on the x axis.

In the above figure, the y axis is extended well below the lowest physiological level of brain cholinesterase activity in order to reach the depth of inhibition produced by donepezil on a continuous basis. Both physiological and donepezil data are expressed as percentage changes from a mean cholinesterase activity which occurs at the rest-activity shifts. It is clear that there is no time during the day that donepezil could be administered that would make a difference in its effect on sleep. The enzyme inhibition is extreme, relative to physiological variation. The normal daily rhythm of enzyme activity, being greater than 40%, varies by a maximum of 8% under donepezil treatment, leaving little difference between day and night, and little difference to be achieved by varying the time of donepezil administration. Thus, Dr Ross's moving the donepezil dose to the morning could not possibly have created the *increased* levels of cholinesterase activity which are required for the rest period.

The extent of the acetylcholinesterase inhibition during donepezil treatment raises a question of how such a powerful alteration of normal physiology is tolerated. Clearly, there must be adaptations in the cholinergic system to such an extreme perturbation.

Investigators in a large study of donepezil administration commented that donepezil-induced side effects "were mild and transient in nature, typically lasting 1-2 days and resolving during continued donepezil use, without dosage adjustment."[4] Although drug administration is daily, plasma levels rise very slowly due donepezil's long half life, and counterregulatory changes in the cholinergic system are able to moderate its effects. Thus, although donepezil inhibits acetylcholinesterase to degrees seen with nerve gases, patients are able to adapt over time.

Thus, the success of Dr Ross' treatment is likely the result of its duration. The patients were given donepezil for one week, and for 3 days, respectively. They were then withdrawn for a week. Subsequently, they were retreated for 2-3 days and were symptomatic, and following which the dose was changed to the morning. It was understood that donepezil side effects abated with continued treatment, and this is the probable explanation for the ultimate disappearance of sleep problems in Dr Ross' patients. It was clear that donepezil's suppression of acetylcholinesterase activity was so extreme that at its minimum, it exerted vastly more cholinesterase inhibition than was

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[4] Burns et al, 1999, The effects of donepezil in Alzheimer's disease – results from a multinational trial, Dement Geriatr Cogn Disord 1999 – copy enclosed.

compatible with sleep, or perhaps life. The success of Dr Ross' treatment can best be explained by his continuing treatment, regardless of the time of administration, and adaptation in his patients.

Reimann

While cholinergic agents, including galantamine, *can* interfere with sleep, whether they *do* interfere with sleep is a function of the plasma level. In the Reimann study, immediate-release galantamine was used. Interference with sleep was evaluated throughout the night for several parameters and occurred only in the first sleep cycle. In Table 3 that the Examiner referred to, SWS NREM 1, REM latency 1, and REM latency 2 were significantly affected by 10 mg galantamine hydrobromide. The definitions for these measures are provided in the last paragraph on page 255. SWS NREM 1, 2 abd 3 are "Amount of SWS (min), determined for the first, second and third NREM cycles. REM latency 1 is the "time from sleep onset (first epoch stage 2) to the first epoch of stage REM", and REM latency 2 is a more complicated definition referring also to the first NREM period, but reduced by certain occurrences. Thus, REM latency 1 defines the actual clock time from the onset of stage 2 sleep to the first REM period. (The two definitions of the first NREM period were used because one was desired, and one was needed for comparability to other publications.)

In subjects receiving 10 mg (the amount desirable for Alzheimer treatment), only the REM latency 2 was significantly affected. As REM latency 2 is the REM latency with some calculations performed, the time period during which this significant effect occurred is the time from sleep onset to the first episode of REM, and is represented by the REM latency 1 definition. It is 70.6 minutes. SWS during the first NREM period is also significantly affected, however that occurs within the time period REM latency 1. To evaluate galantamine's effects later in the night, one must look at measures during subsequent NREM periods. SWS was measured in NREM 2 and 3, there were no significant effects. Thus, the sleep interference of galantamine is confined to the first 98.3 minutes of sleep. (27.7 minutes to the first S2[5], plus 70.6 minutes from S2 to the first REM period = 98.3 minutes) As Reimann's subjects were dosed at 10 pm, one hour before lights out, galantamine's interference with sleep occurred 60 plus 98.3, or 158.3 minutes post dose. To selectively quote that "galanthamine increases the time awake and the number of awakenings", while not taking into account the paper's evidence that sleep effects occur early, and do not occur later in the night, is not to represent Reimann completely. (An effect early in the night may cause an elevation in the mean for the night, while not occurring throughout throughout the night.) Certainly the person who is figuring out how to formulate an extended release galantamine is going to read the whole paper.
The course of plasma levels following 10 mg galantamine hydrobromide p.o. is shown in the figure from Mihailova[6] (below) The plasma galantamine concentrations at which undesirable sleep effects occurred, a little over 2.5 hours, is approximately 0.9μg/ml.

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[5] The S2 latency is the time from lights out to stage 2 sleep)
[6] [6]Mihailova, 1999, previously provided

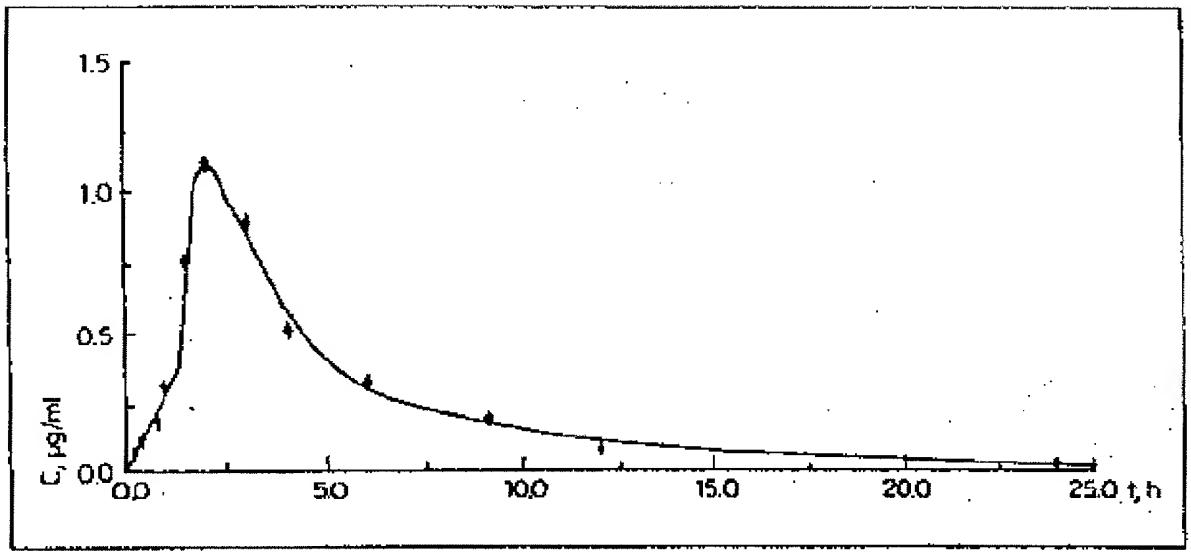

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Fig. 2. Experimentally obtained galanthamine plasma concentrations and theoretical curve, simulated according to model II (two consecutive absorption processes of zero- and first-order). Volunteer 1, dose 10 mg galanthamine-HBr (p.o.).

Mihailova also teaches that the area under the curve following 10 mg galanthamine hydrobromide orally is 4.77 µg.h/ml. Delivering 10 mggalantamine hydrobromide over 8 hours (the desirable dose for Alzheimer's disease) yields steady-state plasma concentrations of 0.6 µg/ml . Thus, plasma galanthamine concentrations would have to be 50% greater than those produced by round the clock level administration of the highest dose used for Alzheimer's disease (24 mg galantamine base per day, = 30 mg galantamine hydrobromide) in order to interfere with sleep This, in combination with the Reimann data, is the information that is needed to design a continuous-release formulation of galantamine. It indicates that the plasma levels achieved by continuous, level release of desirable amounts of galantamine would not have negative effects on sleep.

Conte

Conte is not relevant as there would be no motivation to delay release of galantamine, given the lack of adverse effects at steady-state levels, and there would remain the motivation to avoid fluctuations in acetylcholinesterase inhibition, which were thought to cause drug discontinuations.

It is therefore submitted that against this background, one skilled in the art would not at the time of the present invention have had any reason to go against the teachings of WO88/08708 and take steps to vary the level of acetylcholinesterae inhibitor at various times of the day and so would have had no reason to formulate a dose form as specified in claim 1 or to administer it in the manner specified in claims 41 and 42. It is therefore submitted that no case of *prima facie* obviousness has been made out

The examiner comments that **"No evidence of unexpected results has been proffered."**

(Office Action, page 7). Such evidence is only relevant if a case of prima facie obviousness exists and there is a need to rebut it. As noted above, in the present case, it is submitted that no such *prima facie* case exists.

Nevertheless, the applicant submits the following in support of the above arguments for patentability.

Donepezil produces increases in acetylcholinesterase which are much greater than expected, and account for withdrawal phenomena which are much more serious than expected. In fact, Aricept advertizing now reads "Start with, and stay with Aricept." Aricept's nocturnal stimulation of muscarinic receptors can explain a substantial amount of acetylcholinesterase induction.

Open-label extension studies following pivotal donepezil trials reported that donepezil treatment effects lost after a 6 week discontinuation could not be completely restored by retreatment. [7] [8] This did not occur with a 6 week galantamine withdrawal.[9]

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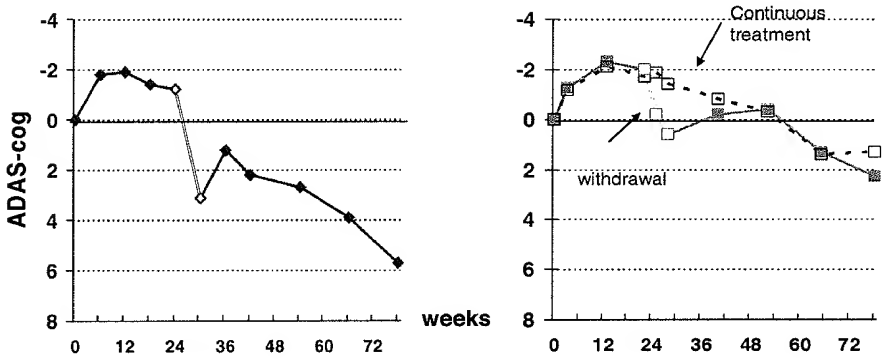
[7] Doody RS, Galdmacher DS, Gordon B et al, Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001; 58:427-433. – copy enclosed.

[8] Burns A, Gauthier S, Perdomo C, Efficacy and safety of donepezil over 3 years: a open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007; 22:806-12. Copy enclosed.

[9] Morris JC, Kershaw P, Cognitive benefits of long-term, continuous galantamine treatment in patients with Alzheimer's disease. Poster presented at the 7th International Geneva/Springfield symposium on Advances in Alzheimer Therapy, Geneva, Switzerland, 3-6 April 2002. Copy enclosed.

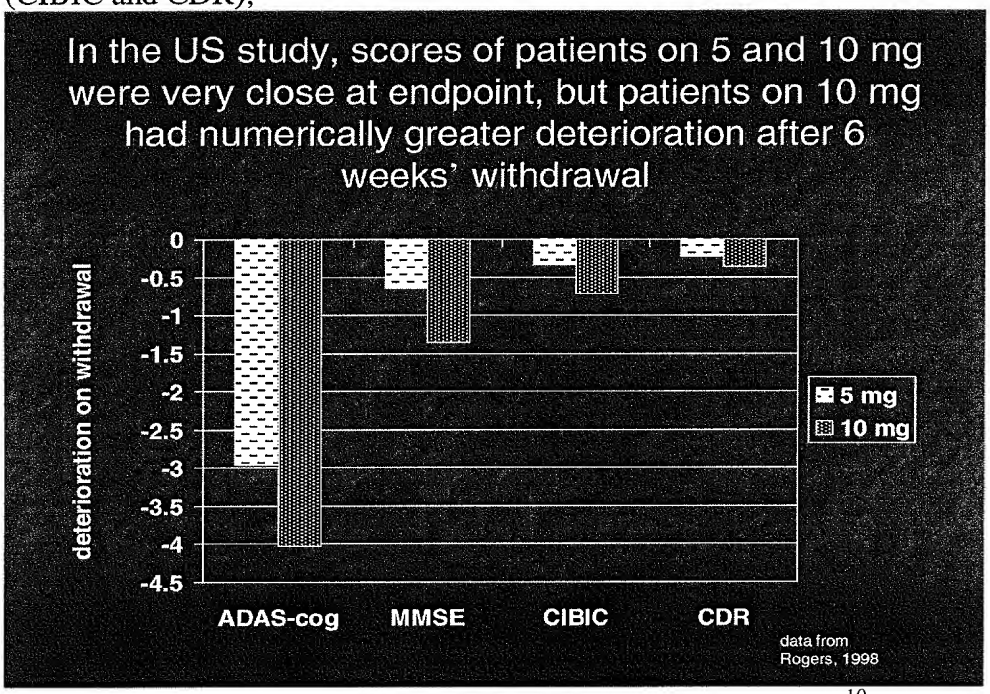
"Donepezil treatment effects that are lost after prolonged discontinuation are not fully recovered when drug treatment is restarted" Doody, 2001

Galantamine retreatment returns patients above baseline to the performance of continuously-treated patients



(Doody, 2001, Morris et al, Poster presented at the 7th Int'l Geneva/Springfield Symposium, Geneva, Switzerland, 3-6 April 2002)

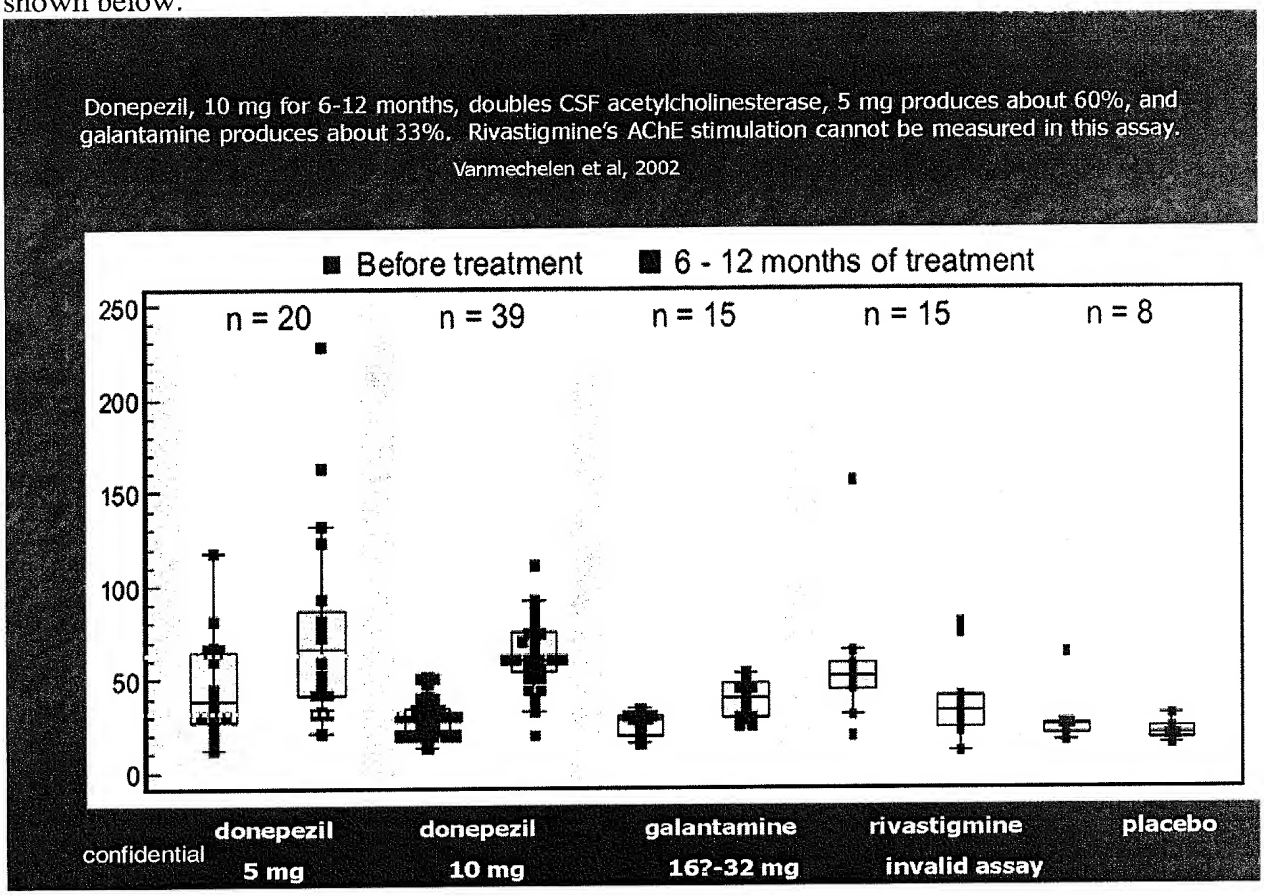
Deterioration in multiple domains, cognitive (ADAS-cog, MMSE) and global (CIBIC and CDR),



was greater in patients discontinued from 10 mg than from 5 mg.[10] A likely

[10] Rogers SL, Farlow MR, Doody RS et al, A 24-week, double-blind, placebo-controlled trial of donepezil

explanation for this difference is the significant difference in the amount of acetylcholinesterase increase in CSF in patients on 10 and compared to 5 mg, as shown below.[11]



Beyond the deterioration during a 6 week withdrawal, it was found that patients withdrawn from 10 mg donepezil had an additional 24 weeks during which there as no significant reduction in nursing home admission, despite donepezil retreatment during this time.[12] Patients who had not had a 6 week withdrawal did have a significant reduction in nursing home placement. Thus, some process initiated during a 6 week withdrawal caused effects for the next 24 weeks which caused patients to be admitted to nursing homes. Such effects are expected to be behavioral and functional, as those are the precipitants for institutionalization of

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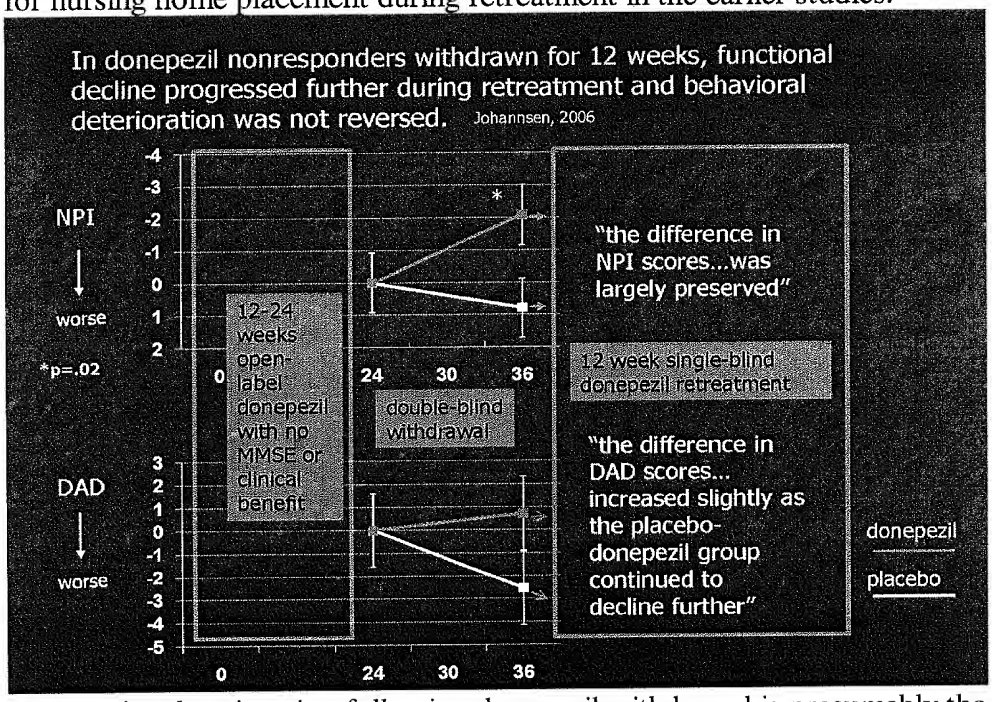
in patients with Alzheimer's disease. Neurology 1998; 50:136-145. Copy enclosed.

[11] VanMechelen E, Andreasen N, Minthon L et al, Effect of cholinesterase inhibitors on Alzheimer's disease biomarkers. Poster presented at 8th International Conference on Alzheimer's Disease and Related Disorders (ICAD), Stockholm, Sweden, July 2002. Copy enclosed.

[12] Geldmacher DS, Provenzano G, McRae T et al, Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003; 51:937-944. Copy enclosed.

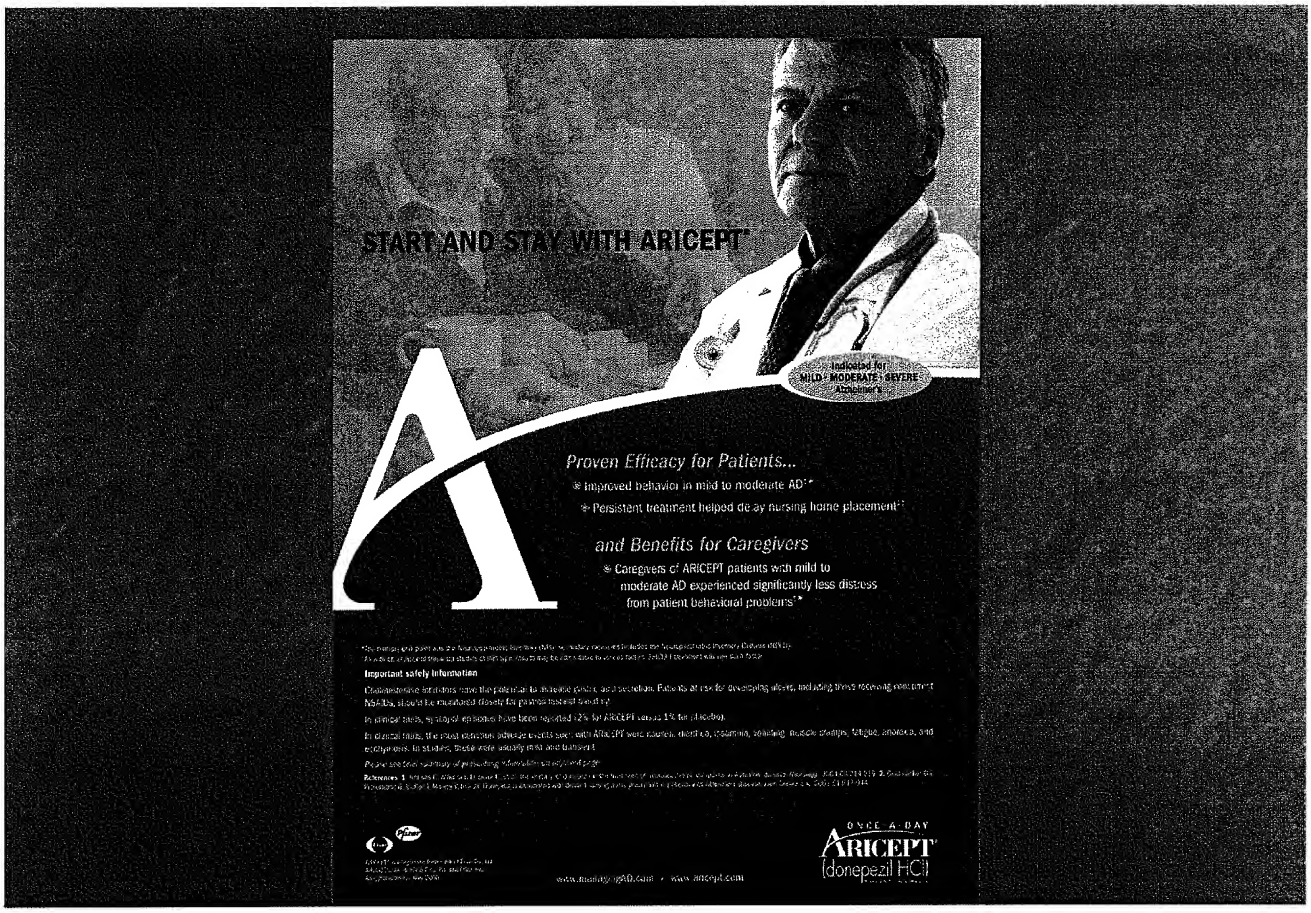
Alzheimer patients.

Behavioral and functional decline occurred during a 12 week withdrawal of patients who had never improved on their donepezil treatment in the Aricept Withdrawal and Readministratin Study, the AWARE study.[13] Behavioral decline was not reversed by donepezil retreatment, and, quite surprisingly, functional decline continued to progress despite retreatment. This is the likely explanation for nursing home placement during retreatment in the earlier studies.



Progressive deterioration following donepezil withdrawal is presumably the reason why Aricept advertizing now reads "Start with and stay with Aricept."

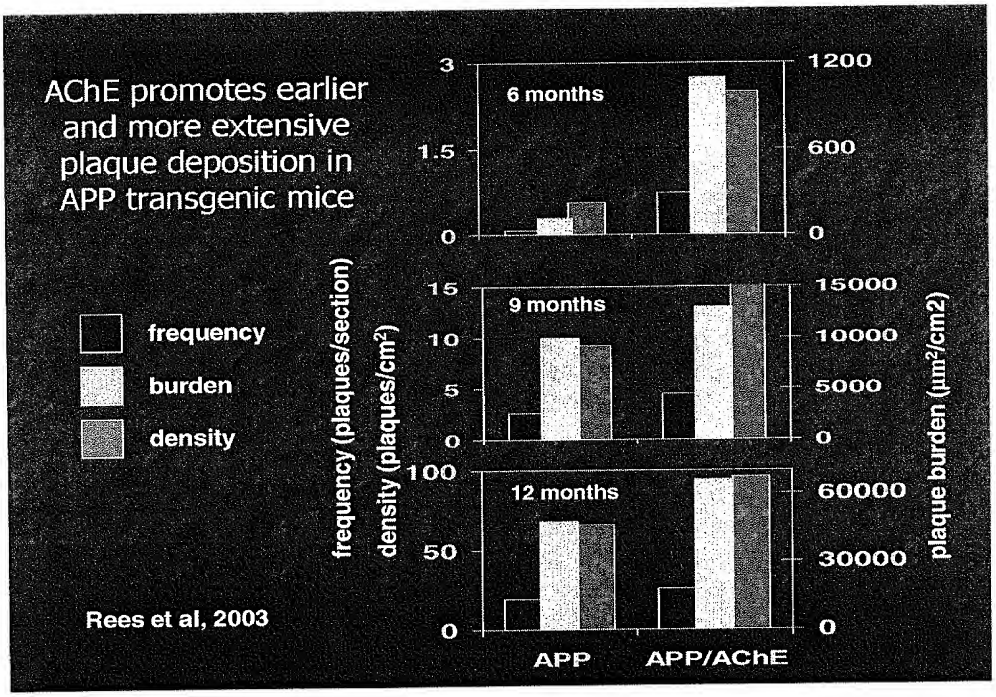
[13] Johannsen P, Salmon E, Hampel H et al, Assessing therapeutic efficacy in a progressive disease. CNS Drugs 2006; 20:311-325. Copy enclosed.



It can be seen, in the middle of the page, that "Persistent treatment helped delay nursing home placement." Thus, the consequences of donepezil withdrawal have now been incorporated in Aricept advertizing.

How does markedly elevated acetylcholinesterase cause persistent deterioration despite donepezil retreatment? This condition has been modeled in transgenic mice. A group of mice transgenic for a human amyloid precursor protein (APP) gene is compared to a group with both APP and extra AChE genes.[14] The group with excess acetylcholinesterase deposits plaque earlier, more densely, and has a greater plaque burden. Thus, excess acetylcholinesterase promotes the pathology of Alzheimer's disease.

[14] Rees T, Hammond PI, Soreq H et al, Acetylcholinesterase promotes beta-amyloid plaques in cerebral cortex. Neurobiology of Aging 2003; 24:777-787. Copy enclosed.



How does nocturnal cholinergic stimulation differentially affect acetylcholinesterase induction? It is known that muscarinic receptors increase in number during rest and that they stimulate transcription factors which activate the acetylcholinesterase gene promoter. (refs) Galantamine, which when administered in the formulations and manner now claimed is at very low levels during the night due to its short half life, has only a minimal effect on CSF acetylcholinesterase in treated humans, but donepezil, which, as had been discussed, greatly inhibits acetylcholinesterase during the night, produced marked increases in CSF acetylcholinesterase. But galantamine is capable of increasing acetylcholinesterase to the same levels as donepezil can, as long as it is given during the rest period.

Galantamine, if administered day and night in rats, can elevate AChE as much as a very long acting AChEI given once a day

Plasma acetylcholinesterase activity

Treatment	N	Percentage of Control ± S.E.M. Day 13	After Washout
Old saline	4	100.0	100.0
Young saline	3	98.4 ± 6.8	100.1 ± 1.6
Donepezil (0.375 mg/kg/day)	4	98.9 ± 3.3	124.1 ± 12.3
Donepezil (0.75 mg/kg/day)	3	82.2 ± 6.0*	121.3 ± 7.4
Galantamine (3.0 mg/kg/day)	3	98.7 ± 7.0	123.5 ± 1.4*
Galantamine (6.0 mg/kg/day)	4	82.8 ± 5.2*	112.7 ± 8.6

* $p < 0.05$ vs. old saline control.

Hernandez et al, 2006

Elevation of acetylcholinesterase by galantamine occurs when rats are dosed twice a day, every 12 hours, so there is as much stimulation during the rest as during the activity period. Thus, nocturnal cholinergic stimulation is capable of increasing acetylcholinesterase. In humans, little galantamine is present during rest, so that acetylcholinesterase elevations are minimal, and withdrawal deterioration is reversible. In the case of donepezil, withdrawal deterioration is not completely reversible and is shown to continue despite retreatment. It was not anticipated that donepezil withdrawal would cause persistent deterioration. However, its occurrence is acknowledged and cautions regarding treatment discontinuation are prominently displayed.

Donepezil was favored because of its long half life and the relative absence of fluctuations in acetylcholinesterase activity. Rogers et al noted "In comparison with the relatively short half-lives of some ChE inhibitors, the long half-life of donepezil (~70 hours) provides relative stability in the extent of AChE inhibition over the course of a day..." (Rogers et al, A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease, Neurology 1998; 50:136-145) It was not expected that by imposing constancy on a system all of whose elements were coordinated to produce a rhythm, the system would try to restore itself, and, in doing so, augment the pathologic processes of Alzheimer's disease. This is why the normal cholinergic rhythm should not be overridden in patients with Alzheimer's disease, as we proposed in 1999.

It is therefore submitted that claims 1, 41 and 42 are therefore not obvious over the cited art. It follows from this that none of the claims dependent on them is obvious.

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The invention as claimed is therefore not obvious and complies with the requirements of 35 USC 103.

In view of the foregoing, it is submitted that this application should be allowed and an early action to this end is respectfully solicited.

Respectfully submitted,

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